## REMARKS

**A. Regarding the Amendments:**

The Applicants request entry of this preliminary amendment. The following Remarks are responsive to the final Office Action mailed June 19, 2001, and the Advisory Action mailed February 12, 2002. Upon entry of this Amendment, claims 1 – 30 will be pending. Claims 1-2, 5 – 7, 10, 11, 14, 20 – 22 have been amended and new claims 23 – 30 have been added as set forth in the attached "Version With Markings To Show Changes Made." Applicants assert that no new matter has been added by these amendments.

Support for the amendment to the claims to recite "human or rodent neuropilin" can be found throughout the Specification as filed. For example, Table 1 on pages 16 and 17 provides support for examples of antisense oligonucleotides designed from the human neuropilin gene sequence and the table legend lists the criteria used to select these oligonucleotides based on a target gene sequence. Figure 5 (SEQ ID NO:33) provides the sequence of a human neuropilin gene sequence, while Figures 5 and 6 (SEQ ID NOs:34 and 35, respectively) provide sequences for rodent neuropilin gene sequences.

Support for the ability of the antisense oligonucleotides of the present invention to inhibit expression of human or rodent neuropilin can be found, for example, in Example 2 at page 42, lines 1 – 20 of the present Specification.

Claims 5, 6, 10 and 14 were further amended to recite an "antisense oligonucleotide from about 20 to about 100 nucleotides in length." Support for this amendment can be found, for example, at page 15, lines 23 – 24, Table 1 on pages 16 and 17, and Examples 3 and 4, page 42, line 21 to page 44, line 17.

Claim 5 was further amended to encompass pharmaceutical compositions comprising analogs of the antisense oligonucleotide. Support for this amendment can be found, for example, at page 12, line5 to page 14, line 24.

New claims 23 – 25 were added to claim an alternative embodiment of the present invention, which is a method of inhibiting cancer cell growth "comprising, contacting said cancer cells in vitro" with the claimed antisense oligonucleotide. Support for the subject matter of the new claims can be found throughout the Specification as filed, for example, in Example 1 at page 41, lines 3 – 26 and the data presented in Figures 1A – 1F.
New claims 26 – 30 specify an antisense oligonucleotide complementary to a disclosed cDNA sequences, and methods and compositions that use the antisense oligonucleotide.
The Examiner's bases for rejecting claims 1 – 16 and 19-22 are addressed below. The foregoing amendments are made without any intention to abandon the subject matter of the claims as filed, but with the intention that claims of the same, lessor, or greater scope may be pursued in the present application or in a continuation, continuation-in-part, or divisional application.

**B. Rejection under 35 U.S.C. §112, first paragraph, written description**:

The Examiner has rejected Claims 1 – 5 under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not adequately described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Paper 13, page 2.) Applicants respectfully traverse, and obviate-in-part, this objection.

As indicated by the Examiner on page 2 of Paper 13, the present specification teaches SEQ ID NOs:1-30 as antisense oligonucleotides to a human neuropilin gene and provides the sequences of rat and mouse neuropilin genes. Applicants assert that the disclosure of these sequences combined with the teaching of the present invention would allow one skilled in the art

to make and use the claimed invention. Furthermore, Applicants submit that the teaching of the target neuropilin gene in human, mouse and rat would be considered to be a representative number of species to one skilled in the relevant art. In order to expedite prosecution, however, Applicants have amended claims 1, 4 and 5 to specify that the antisense oligonucleotide comprises a sequence complementary to a transcribed region of a human or rodent neuropilin gene.

Applicants reserve the right to pursue the withdrawn subject matter in the present application or in a continuation, continuation-in-part, or divisional application. In view of the present amendment and remarks, Applicants respectfully submit that the subject matter of amended claims 1 – 5 is clearly and fully described in the Specification and request withdrawal of this §112 rejection.

**C. Rejection under 35 U.S.C. §112, first paragraph, enablement:**

The Examiner has rejected Claims 5 – 16 and 19 – 22 under 35 U.S.C. §112, first paragraph, because the Specification allegedly does not provide enablement for the claimed subject matter. (Paper 13, pages 3 to 4.) Applicants respectfully traverse, and obviate-in-part, this rejection.

The Examiner has indicated that the Specification is enabling for methods of inhibiting the expression of the disclosed sequence of human neuropilin in cells in culture and via injection of the specific disclosed sequences which were used in the treatment of tumor cells in mice.

Applicants respectfully submit that Specification further enables methods of inhibiting the growth of cancer cells in vitro and in vivo by administering an antisense oligonucleotide against a neuropilin gene. In order to expedite examination, however, Applicants have amended claims 5, 6, 10 and 14 to recite an antisense oligonucleotide that is about 20 to about 100

nucleotides in length and comprises a sequence complementary to a transcribed region of a human or rodent neuropilin gene. Applicants reserve the right to pursue the withdrawn subject matter in the present application or in a continuation, continuation-in-part, or divisional application.

Applicants submit that the pharmaceutical composition of claims 5 and 19, which contains an antisense oligonucleotide of from about 20 to about 100 nucleotides in length and a sequence that is complementary to a transcribed region of a human or rodent neuropilin gene, is fully enabled by the present Specification. For example, the Specification contains a detailed description of the formulation of pharmaceutical compositions comprising the antisense oligonucleotides of the present invention and methods for their administration to mammals (e.g. page 25, line 15 – page 34, line 14). Furthermore, Example 3 of the present invention (See page 42, line 21 to page 43, line 26) provides a demonstration of the use of an of antisense oligonucleotide according to the present invention in a pharmaceutical composition. Therefore, Applicants assert that a worker skilled in the art given the teaching of the present application would be able to make and use the claimed pharmaceutical composition without undue experimentation.

Applicants further submit that the present Specification provides enablement for the methods of claims 6 – 16 and 20 – 22, which comprise administering an antisense oligonucleotide of from about 20 to about 100 nucleotides in length and a sequence that is complementary to a transcribed region of a human or rodent neuropilin gene.

Applicants respectfully submit that a worker skilled in the art, having regard to the present Specification, would not require undue experimentation in order to design and use antisense oligonucleotides against a human or rodent neuropilin gene. The experimental evidence provided in Examples 3 and 4 of the present application is such that a worker skilled in

the relevant art wound be convinced that the claimed antisense oligonucleotides would be useful in the treatment of cancer cells in a whole organism, which is a human or a rodent. As indicated in Applicants' response to the previous Office Action, the animal models used in Examples 3 and 4 are art recognized models used to demonstrate efficacy of antisense oligonucleotides in the treatment of tumors and the data produced using these models is known to have a reasonable correlation with in vivo activity in humans. Therefore, Applicants assert that the methods of claims 6 – 16 and 20 – 22 are fully enabled by the present Specification.

In view of the present amendments and remarks, Applicants respectfully request withdrawal of this §112 rejection.

The Examiner has objected to claims 17 and 18 and being dependent upon a rejected base claim. (Paper 13, page 7.) Applicants assert that the base claims are allowable and respectfully requests withdrawal of this objection.

## CONCLUSION

On the basis of the foregoing claim amendments and remarks, Applicants respectfully submit that, upon entry, the pending claims will be in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

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## EXHIBIT A: VERSION WITH MARKINGS TO SHOW CHANGES MADE

**In the claims:**

Please amend the claims as follows:

1. (Twice Amended) An antisense oligonucleotide, or analog thereof, from about 7 to about 100 nucleotides in length comprising a sequence complementary to a transcribed region of a human or rodent neuropilin gene, wherein said oligonucleotide, or analog thereof, specifically binds to a nucleic acid comprising a sequence corresponding to said transcribed region and inhibits human or rodent neuropilin expression.

2. (Amended) The antisense oligonucleotide, or analog thereof, of Claim 1 further comprising one or more phosphorothioate internucleotide linkages.

3. (Twice Amended) The antisense oligonucleotide, or analog thereof, of Claim 1 further comprising additional nucleotides not complementary to the transcribed region of [a] the neuropilin gene.

4. (Twice Amended) A vector comprising an oligonucleotide sequence from about 7 to about 100 nucleotides in length comprising a sequence complementary to a transcribed region of a human or rodent neuropilin gene, wherein said oligonucleotide, or analog thereof, specifically binds to a nucleic acid comprising a sequence corresponding to said transcribed region and inhibits human or rodent neuropilin expression.

5. (Twice Amended) A pharmaceutical composition comprising a pharmaceutically acceptable excipient and an effective amount of [the] an antisense oligonucleotide, or analog thereof, from about [7] 20 to about 100 nucleotides in length comprising a sequence complementary to a transcribed region of a human or rodent neuropilin gene, wherein said

oligonucleotide, or analog thereof, specifically binds to a nucleic acid comprising a sequence corresponding to said transcribed region and inhibits human or rodent neuropilin expression.

6. (Twice Amended) A method for inhibiting the growth of a [mammalian] human or rodent tumor comprising, administering to a [mammal] human or rodent suspected of having the tumor an effective amount of an antisense oligonucleotide, or analog thereof, from about [7] 20 to about 100 nucleotides in length comprising a sequence complementary to a transcribed region of a [mammalian] human or rodent neuropilin gene under conditions such that the growth of the tumor is inhibited, wherein said [olignucleotide] oligonucleotide, or analog thereof, specifically binds to a nucleic acid comprising a sequence corresponding to said transcribed region.

7. (Amended) The method according to Claim 6 further comprising the step of administering to the [mammal] human or rodent a chemotherapeutic agent.

10. (Twice Amended) A method for inhibiting the metastasis of a [mammalian] human or rodent tumor comprising, administering to a [mammal] human or rodent suspected of having a metastatic tumor an effective amount of an antisense oligonucleotide, or analog thereof, from about [7] 20 nucleotides to about 100 nucleotides in length comprising a sequence complementary to a transcribed region of a [mammalian] human or rodent neuropilin gene under conditions such that the metastasis of the tumor is inhibited, wherein said [olignucleotide] oligonucleotide, or analog thereof, specifically binds to a nucleic acid comprising a sequence corresponding to said transcribed region.

11. (Amended) The method according to Claim 10 further comprising the step of administering to the [mammal] human or rodent a chemotherapeutic agent.

14. (Twice Amended) A method for inhibiting neovascularization comprising, administering to a [mammal] human or rodent an effective amount of an antisense oligonucleotide, or analog thereof, from about [7] 20 nucleotides to about 100 nucleotides in length comprising a sequence complementary to a transcribed region of a [mammalian] human or rodent neuropilin gene under conditions such that neovascularization is inhibited, wherein said [olignucleotide] oligonucleotide, or analog thereof, specifically binds to a nucleic acid comprising a sequence corresponding to said transcribed region.

20. (Amended) The method according to Claim 8, [wherein said mammal is] comprising administering said antisense oligonucleotide to a human.

21. (Amended) The method according to Claim 13, [wherein said mammal is] comprising administering said antisense oligonucleotide to a human.

22. (Amended) The method according to Claim 16, [wherein said mammal is] comprising administering said antisense oligonucleotide to a human.

Please add the following new claims:

--23. (New) A method of inhibiting the growth of cancer cells comprising, contacting said cancer cells in vitro with an effective amount of an antisense oligonucleotide, or analog thereof, from about 7 to about 100 nucleotides in length comprising a sequence complementary to a transcribed region of a human or rodent neuropilin gene under conditions such that the growth of the cancer cells is inhibited.

24. (New) The method according to claim 23, wherein the oligonucleotide is from 20 to about 100 nucleotides in length and comprises a sequence selected from the group consisting of SEQ ID NOs:1 - 30.

25. (New) The method according to Claim 23 wherein the oligonucleotide is nuclease resistant.

26. An antisense oligonucleotide, or analog thereof, from about 7 to about 100 nucleotides in length comprising a sequence complementary to a transcribed region of a neuropilin gene, wherein said transcribed region has a sequence as set forth in any one of SEQ ID NOs:33 - 35 and wherein said oligonucleotide, or analog thereof, specifically binds to a nucleic acid comprising a sequence corresponding to said transcribed region and inhibits neuropilin expression.

27. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and an effective amount of the antisense oligonucleotide, or analog thereof, according to Claim 26.

28. A method for inhibiting the growth of a human or rodent tumor comprising administering to a human or rodent suspected of having the tumor an effective amount of the antisense oligonucleotide, or analog thereof, according to Claim 26.

29. A method for inhibiting the metastasis of a human or rodent tumor comprising administering to a human or rodent suspected of having a metastatic tumor an effective amount of the antisense oligonucleotide, or analog thereof, according to Claim 26.

30. The method according to Claim 28 or 29, comprising administering said antisense oligonucleotide, or analog thereof, by infusion. --